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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 80.WO1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/038920	International filing date *(day/month/year)* 18.11.2004	Priority date *(day/month/year)* 21.11.2003

International Patent Classification (IPC) or national classification and IPC
C07D307/68, C07D409/04, C07D409/10, A61K31/381, A61P3/06

Applicant
ARENA PHARMACEUTICALS, INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 14 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.06.2005	01.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/038920

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-67 as originally filed

Sequence listings part of the description, Pages

65-67 as originally filed

Claims, Numbers

1-48 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27-37

because:

☒ the said international application, or the said claims Nos. 27-37 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9,10,12-16,18-22,26,30-31,42,46
	No:	Claims	1-8,11,17,23-25,27-29,32-41,43-45,47-48
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	1-26,38-48
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/038920

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

The application is directed to

(i) 4-oxo-4,5-dihydro-furan-2-carboxylic acid derivatives (I) (claims 1-24),

(ii) a pharmaceutical composition comprising a compound (I) (claims 25-26),

(iii) the corresponding therapeutic methods (claims 27-37),

(iv) the medical use of compounds (I) (claims 38-47), and

(v) a method for producing a pharmaceutical composition with a compound (I) (claim 48).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 27-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

See item V.3 below.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WISE, A. ET AL. JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 11, 14 March 2003, pages 9869-9874.

D2: JIRKOVSKY, I.; CAYEN, M. N. J. MED. CHEM., vol. 25, no. 10, 1982, pages 1154-1156.

D3: WO 80/00025 A, 10 January 1980.
D4: US-A-4 244 958, 13 January 1981.
D5: KALLAI-SANFACON, M. A. ET AL. PROC. SOC. EXP. BIOL. MED., vol. 173, 1983, pages 367-371.
D6: US 2004/142377 A1, 22 July 2004.
D7: CAINE, D. S.; PAIGE, M. A. SYNLETT, vol. 9, 1999, pages 1391-1394.
D8: MEISTER, H.; PEITSCHER, G. LIEBIGS ANN. CHEM., 1974, pages 1908-1914.

D6 was published after the priority date. Under the presumption that the priority is valid for the claimed matter the said document is not considered as prior art under Rule 64.1 PCT.

2 Novelty

2.1 The present claims 1-8, 11, 17, 23-25, 27-29, 32-41, 43-45, 47, and 48 lack novelty in view of one or more of the documents **D2** to **D4**.

2.2 **D1** relates to the molecular identification of high and low affinity receptors for nicotinic acid. In this context the document identified 4-oxo-5-methyl-5-phenyl-4,5-dihydrofuran-2-carboxylic acid (acifran), a compound reported to produce a pharmacological effect resembling that of nicotinic acid, as a full agonist of such nicotinic acid receptor (**D1**, page 9873, last paragraph, to page 9874, first paragraph). **D5**, similarly, refers to the lipid-lowering properties of 4-oxo-5-methyl-5-phenyl-4,5-dihydrofuran-2-carboxylic acid in normal and hyperlipidemic rats. The document mentions that the compound lowers serum triglyceride, free fatty acid and LDL cholesterol concentrations, and it is concluded that it's mode of action resembles that of nicotinic acid. **D1** and **D5** are not relevant to the question of novelty of the application, because acifran (i.e. the compound according to the present formula (I) with $R^1 = R^2 = H$, R^3 = phenyl, and R^4 = methyl) is not comprised within the present claims.

D2 to **D4** relate to hypolipidemic 4-oxo-4,5-dihydro-furan-2-carboxylic acid derivatives (**D2** to **D4**), the corresponding pharmaceutical compositions and therapeutic methods

of lowering lipid levels in a mammal (**D3**, claims 23, 26; **D4**, claims 27-28). **D2** discloses a present compound (I) wherein R^1 and R^2 is hydrogen, R^3 is substituted phenyl (i.e. 4-chlorophenyl) and R^4 is methyl (**D2**, compound **5c**), thereby resulting in a lack of novelty of present claims 1, 4-7, 11, and 17. Furthermore, the present compounds (I) substantially overlap with the compounds of **D3** and **D4** when R^1 and R^2 are H or C_{1-6}alkyl (**D3/D4**: R^3 and R^4); R^3 is aryl, substituted phenyl, 2-chlorophenyl, and 3-chlorophenyl (**D3/D4**: R^1); and R^4 is ethyl, n-propyl, C_{4-6}alkyl, and C_{1-6}alkyl (**D3/D4**: R^2). In addition, both document disclose already a specific compound within the overlapping range (**D3/D4**: claim 7 each). The present claims 1-8, 11, 17, 23-25, 27-29, 32-41, 43-45, 47, and 48 lack thus novelty for the whole overlapping range with the document **D3** and **D4**. In this context it is noted that the teaching of **D3** and **D4** is not merely limited to the specific examples.

D7 and **D8** show 2-methyl-furan-4-ones bearing a cyclopropyl (**D7**, compounds **5a/5b**) or a heterocycloalkenyl (**D8**, compound **3**) in the present position R^3. As these compounds are 2-methyl rather than 2-carboxy furanones, **D7** and **D8** are not relevant to the question of novelty of the application.

2.3 **D6** relates to a method of identifying whether a compound is a modulator of a nicotinic acid GPCR. Furthermore it is directed to a modulator, preferably an agonist, of a nicotinic acid receptor RUP25 identified according to said method. Although, the present compounds (I) are not disclosed in **D6**, it may become relevant to the question of inventive step if the present claimed date of priority was not valid.

3 Unity of Invention

The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to five separate inventions not linked together by a common underlying inventive concept as required by Rules 13.1 and 13.2 PCT. The claims and inventions to which the separate inventions relate are grouped as follows (in the order chosen by the applicant).

(1) Claims 1-5 and 23-48 (all part) directed to compounds (I) wherein R^3 is unsubstituted aryl and R^4 is H; as well as subject matter referring to such compounds

(I).

(2) Claims 1-5, 6-10, and 22-48 (all part) directed to compounds (I) wherein R^3 is unsubstituted aryl and R^4 is ethyl, n-propyl, C_{4-6}alkyl or C_{1-6}haloalkyl; as well as subject matter referring to such compounds (I).

(3) Claims 1-11, 17, 21-48 (all part) and claim 16 (complete) directed to compounds (I) wherein R^3 is C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl; as well as subject matter referring to such compounds (I).

(4) Claims 1-11, 17, 21-48 (all part) and claims 12-13, 15, 19, 20 (all complete) directed to compounds (I) wherein R^3 is heteroaryl, C_{3-7}heterocycloalkyl or C_{3-7}heterocycloalkenyl; as well as subject matter referring to such compounds (I).

(5) Claims 1-11, 17, 21-48 (all part) and claims 14, 18 (all complete) directed to compounds (I) wherein R^3 is substituted aryl, substituted phenyl, 2-chlorophenyl, 3-chlorophenyl or naphthyl; as well as subject matter referring to such compounds (I).

The identified inventions involve the technical feature of a "5-(R^3,R^4)-substituted 4-oxo-4,5-dihydro-furan-2-carboxylic acid" as the sole common link. However, this feature cannot be accepted to constitute a special technical feature because it does not define a contribution over the prior art. The document **D1** discloses already that the compound acifran (i.e. a compound according to present formula (I) wherein R^1 = R^2 = H, R^3 = phenyl, and R^4 = methyl) is as an agonist at a nicotinic acid receptor. Starting from this document the problem underlying the present application may be seen in the provision of further 4-oxo-4,5-dihydro-furan-2- carboxylic acid derivatives as nicotinic acid receptor agonists. The contributions claimed in the present application which are possibly made over the prior art are:

(a) the provision of further nicotinic acid receptor agonists by replacing the (R^4)methyl group in acifran of **D1** with H;

(b) the provision of further nicotinic acid receptor agonists by replacing the

(R^4)methyl group in acifran of **D1** with a substituent having two ore more non-hydrogen atoms;

(c) the provision of further nicotinic acid receptor agonists by replacing the (R^3)phenyl group in acifran of **D1** with a non-aromatic carbocyclic group;

(d) the provision of further nicotinic acid receptor agonists by replacing the (R^3)phenyl group in acifran of **D1** with a heterocyclic group; and

(e) the provision of further nicotinic acid receptor agonists by replacing the (R^3)phenyl group in acifran of **D1** with a substituted aryl group.

These contributions, however, have nothing more in common than each single of these contributions has in common with the prior art. Hence, starting from **D1** these contributions diverge in five different directions and are, thus, not so linked as to form one single inventive concept, which would support the unity of the invention.

4 Inventive Step

Insofar as the application relates to novel subject matter the following observations would apply to the requirements of inventive step.

4.1 The application describes the synthesis of certain compounds (I) and states vaguely that "certain compounds of the invention have an EC_{50} in the range of about 30 nM to about 30 µM" (page 49, lines 21-22).

4.2 **D1** discloses that 4-oxo-5-methyl-5-phenyl-4,5-dihydrofuran-2-carboxylic acid (acifran; present formula (I) with $R^1 = R^2 = H$, R^3 = phenyl, and R^4 = methyl), a compound known to produce a pharmacological effect alike nicotinic acid, is a nicotinic acid receptor full agonist. Starting from **D1** as most relevant state of the art the problem underlying the application may thus be seen in the provision of further nicotinic acid receptor agonists.

4.3 Invention (1) as defined under item V.3 above

The compounds according to the aspect (1) of the present application differ from acifran of **D1** insofar as the they bear in position R^4 a hydrogen atom rather than a methyl group. In addition, the documents **D2** to **D4** disclose hypolipidemic 4-oxo-4,5-dihydro-furan-2-carboxylic acid derivatives including acifran. These compounds, however, appear to require at least one carbon atom in position R^4 for their hypolipidemic activity. For that reason it does not appear that the skilled person would have reasonable expectation of success in modifying acifran of **D1** in order to arrive at the present (R^4)hydrogen compounds (I) whilst maintaining the desired activity. For that reason the subject matter of the aspect (1) of the application, in principle, might involve an inventive step.

See, however, the objections raised under items V.4.6 and V.4.7 below.

4.4 Inventions (2), (3), and (5) as defined under item V.3 above

The compounds of the aspect (2) differ from acifran of **D1** in bearing in position R^4 instead of a methyl group a substituent with at least two non-hydrogen atoms. The compounds of the aspect (3) differ from said acifran in bearing in position R^3 a non-aromatic carbocyclic rather than a phenyl group; and the compounds of the aspect (5) differ from acifran in bearing in position R^3 a substituted aryl or phenyl group rather than unsubstituted phenyl. Such compounds are already taught in one or more of the documents **D2** to **D4** (cf. e.g. **D3**, claim 1: R^1/R^2 = lower alkyl, cyclo(lower)alkyl, and phenyl mono- or disubstituted with ...) and known to exhibit hypolipidemic activity alike acifran disclosed in documents **D1** to **D4**. Starting from **D1** in combination with one of the documents **D2** to **D4**, the compounds according to the aspects (2), (3), and (5) represent merely obvious alternatives of acifran of **D1**. In the absence of any substantiated unexpected effect(s) of those compounds of the aspects (2), (3), and (5), which are structurally closest related to acifran, in comparison with acifran of **D1**, no inventive activity would be seen in the aspects (2), (3) and (5) of the application.

In addition, see item V.4.7 below.

4.5 Invention (4) as defined under item V.3 above

The compounds of the aspect (4) differ from acifran of **D1** in bearing in position R^3 instead of phenyl a heterocyclic group. It does not appear that any of the cited documents hints or suggests that the (R^3)phenyl group may be replaced with a heterocyclic group whilst maintaining the desired activity. For that reason the subject matter of the aspect (4) of the application, in principle, might involve an inventive step.

See, however, the objections raised under items V.4.6 and V.4.7 below.

4.6 At present, however, the application does not provide any substantiation that the technical problem has been really solved by the compounds of the aspects (1) and (4) of the application. Under these circumstances, the only basis for accepting that the claimed compounds would solve the problem posed, would be common general knowledge. The same common general knowledge, however, would be similarly applicable to the assessment whether the solution of the technical problem is to be considered obvious. Consequently, in the absence of any substantiation of the technical effect and any instructions how said effect has been assessed, no inventive step would be acknowledged for the subject matter of the aspects (1) and (4).

4.7 If the applicant was able to substantiate that the compounds of the aspect (1) and (4) provide a solution of the problem underlying the application, or to substantiate an unexpected effect for certain of the compounds of the aspects (2), (3), and (5) in comparison with acifran, then it is also reminded that the breath of the claims should be such that it represents a plausible generalization over the examples provided, and such that it is credible that substantially all compounds falling within its scope actually provide a solution to the problem underlying the invention. In this context it is noted that the terms such as "aryl", "heteroaryl", "substituted", etc. used in the claims are open-ended and thus likely to comprise structures which will not solve any relevant technical problem. Hence, no inventive step would be acknowledged for such open-ended compounds and subject matter referring to them.

4.6 For these reasons, the claims 1-48 do at present not meet the requirements of inventive step.

4 Industrial Applicability

For the assessment of the present claims 27-37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
US 2004/142377 A1	22.07.2004	06.12.2002	12.03.2002

Re Item VII
Certain defects in the international application

The relevant background art disclosed in **D1** to **D4** is not mentioned in the description, nor are these documents identified therein (Rule 5.1(a)(ii) PCT).

Re Item VIII
Certain observations on the international application

The application does not comply with the requirements of Article 6 PCT for the following reasons.

1 The difference between "unsubstituted aryl" and "naphthyl" as defined in claim 1 for R^3 as well as the difference between "substituted aryl" and "substituted phenyl, 2-chlorophenyl, 3-chlorophenyl, and naphthyl" as defined in claim 1 for R^3 is at present not evident, thereby resulting in a lack of clarity of the claim.

2 The term "metabolic-related disorder" used in claims 27, 32, 39, and 44 has no clear meaning and renders the said claims unclear (Article 6 PCT).

3 The statement on page 63, line 37 to page 64, line 2 implies that the subject matter for which protection is sought might be different from what is defined in the claims, thereby resulting in a lack of clarity of the claims and the application.